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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,870	ROMANS, MARY H.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *10-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-4 and 6-9 in the election received 07/01/2003 is acknowledged. The traversal is on the ground(s) that Groups I-IV are related and are not patentably distinct. More specifically, Applicant argues that the methods of Group III can only be performed using the methods of Groups I and II and that the composition of Group IV is dependent upon the animal model of Groups I and II. These arguments are not found persuasive.

With respect to Groups I and II, the inventions are distinct if the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the animal model of Group II does not require the methods of Group I. With respect to Groups II and IV, the inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions or different effects (MPEP 806.04 and MPEP 808.01). Group II is drawn to an animal model of pain. Group IV is drawn to a composition for treating pain. These products are not disclosed as capable of use together, they have different modes of operation, and are used for a different function or purpose. Furthermore, the methods of Group III do not require the method of producing nerve alterations of Group I and Group III has distinct method steps that are unrelated and do not require the method steps of Groups I or II. No method step of Groups I or II are required for any method step of Group III. Furthermore, the methods of Group III can be carried out using any model of pain, or even a wild-type animal. The composition of Group IV is not dependent upon the method of making an animal model of Groups I and II. Neither the methods of Groups I and II

nor the product made by those methods are necessary for the composition of Group IV.

Applicant also argues that the search burden of Groups I-IV would be reasonable because they are related. This is not persuasive because it would require undue burden to search a method of making an animal model and compositions for treating pain together. The compositions are only related in that they could possibly be used to treat symptoms exhibited by the animal made by the methods of Group I. The compositions could be used to treat pain in animals other than the claimed animal model (Group II) made by the methods of Group I. The compositions of Group IV do not rely upon the methods of screening of Group III.

Applicant further argues that claims 10 and 11 should be considered. Claims 10 and 11 were not considered in the restriction requirement because they are wholly unclear. Claim 10 is drawn to a product of any of the processes of claims 6-9. Claim 11 is drawn to the product of claim 10 wherein the product is a drug, treatment or cell assay. As written, claim 10 is drawn to a nerve alteration, as it is the product of the method of producing a nerve alteration (claims 6-9). However, in light of claim 11, encompassing drugs, treatments and assays, it cannot be determined what Applicant is intending to claim in either of claims 10 and 11. A treatment is not a product that results from a method of producing a nerve alteration. Furthermore, claims to drugs and assays are patentably distinct themselves. Therefore the breadth of the claims is so large, that it cannot be determined what Applicant is claiming.

The requirement is still deemed proper and is therefore made FINAL.

However, in light of Applicant's request, Groups I and II will be examined together.

Claims 12-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the response received 07/01/2003. Claims 1-17 are pending and claims 1-9 are under consideration in the instant office action.

Claim Objections

Claim 8 is objected to because of the following informalities:

Claim 8 appears to have a typographical error. In line 5, the claim reads, "...where the gel is collagen" rather than "...wherein the gel is collagen."

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 5 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The animal model of claim 5 can be read to encompass a human having a compression of a nerve. A human being is non-statutory subject matter. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a non-human mammal comprising non-traumatically and non-surgically compressing the tibial nerve such that allodynia is achieved or compressing the saphenous nerve via a surgical procedure such that hyperalgesia is achieved, does not reasonably provide enablement for any other species of animal made by non-traumatically altering any nerve using any means of altering such that any sign or symptom of persistent neurogenic pain is achieved. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-4 and 6-9 are drawn to a method for producing nerve alterations in an animal. Claim 5 is drawn to an animal model for pain wherein compression is placed around a nerve.

The specification has taught making an animal model of persistent neurogenic pain by injecting collagen into the left posterior leg of a mouse, around the tibial nerve (page 15, 2nd paragraph; page 22, last paragraph-page 23). The specification has also taught making a rat model (pages 21-22) and guinea pig model (page 23, last paragraph-page 24) by making a surgical incision and injecting collagen around the saphenous nerve. The mouse model was used in the von Frey method of assessing sensitivity to light touch in determining pain behavior (page 14, 2nd paragraph) and the guinea pig model was used in pinprick testing (page 24). The specification prophetically teaches using the rat model in light touch, pinprick, ant heat and cold assays (page 22, 2nd paragraph). Results of these assays were not reported.

1) Claims 1-9 encompass transgenic animals as well as animal injected with substances other than collagen that can cause compression of a nerve. The claims merely require that a

nerve be non-traumatically altered (claims 1-4), compressed (claims 6-9) or compressed non-surgically (claim 5). The breadth of the claims, therefore, encompasses transgenic animals expressing a gene that can indirectly cause nerve compression, for example by causing inflammation around the nerve. Claims also encompass injection of a substance, a chemical or nucleic acid, that causes alteration of a nerve such that persistent pain results (claims 1 and 4). It is noted that the preamble of claim 1 recites "nondestructive nerve alteration". The method steps of the claim do not contain this limitation. Furthermore, as written, the term nondestructive in the preamble of the claim could describe the nerve alterations as being non-destructive to the animal or to something other than the nerve. Therefore, the term "nondestructive" is not necessarily indicative that the alteration was nondestructive to the nerve and the claim, therefore, encompasses any non-traumatic nerve alteration.

The specification has taught compressing a nerve by injecting collagen around the nerve such that the nerve is compressed, causing persistent pain (for example see page 14, 2nd paragraph –page 17, 2nd paragraph), or a sign or symptom thereof. The specification has not provided any guidance with respect using transgenesis or injection of any substance other than collagen to generate an animal model for persistent neurogenic pain.

The art of transgenic animals has for many years held that the phenotype of transgenic animals is unpredictable due, in part, to the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a

transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 273-276). With respect to injection of substances other than collagen, for example, one could imagine injection of a substance that causes constant neuron firing or an immune response that causes compression or destruction of a nerve. For example, Wang (2003, Advanced Drug Delivery Reviews, Vo. 55, pages 949-965) taught that nearly half of human neuropathies are caused by inflammation or infection rather than trauma (page 954, 2nd paragraph). Furthermore, Eliav demonstrated that inflammation of the sciatic nerve could be induced to cause peripheral neuropathies (1999, Pain, Vol. 83, pages 169-182).

The specification fails to provide any guidance with respect to altering a nerve using transgenesis or injection of a substance other than collagen that would directly or indirectly cause compression of a nerve as broadly encompassed by claims 1,4 and 5. The specification has not taught any gene, promoter or site of integration that would result in alteration or compression of a nerve through any mechanism, i.e. induced swelling of the nerve or around the nerve or neural degradation. The specification fails to provide guidance as to what substances might elicit an immune response or any other response that results in alteration or compression of a nerve such that a sign or symptom of a physiologic change in the nerve that is indicative of persistent neurogenic pain. In light of the state of the art with respect to the unpredictability of transgenesis and the breadth of the claims with respect to injection of substances other than collagen, and in light of the lack of guidance in the specification with respect to generating transgenic animals or injection of substances other than collagen, it would require one of skill in the art undue experimentation to determine how to generate the animals broadly encompassed by the claims.

2) Claims 1-9 encompass any species of animal, including invertebrates with primitive nervous systems. The specification has taught compressing a nerve by injection of collagen in mammals, including rat, mouse and guinea pig. The specification has not taught how to compress, or alter in any manner, a nerve in any non-mammalian species. Specifically, for example, coelenterates have a very primitive nervous system consisting of a nerve net of neural cells rather than nerves as encompassed by the claims (Keeton, W and Gould, J., Biological Science, 4th edition, W.W. Norton and Company, paragraph bridging pages 458-459). One of skill in the art cannot alter a nerve in an animal that does not comprise a nerve, per se.

The specification has not provided the guidance necessary to non-traumatically and non-surgically alter any structure analogous to a mammalian nerve in any non-mammalian species. The specification has not provided any guidance with respect to using collagen to compress a neural cell in a nerve net or any other structure analogous to a nerve. The specification has not provided any guidance with respect to assessing pain in any non-mammalian animal. For example, the specification does not teach how one would one perform the pinprick test on a jellyfish. Therefore, it would require undue experimentation for one of skill in the art to determine how to non-traumatically and non-surgically alter a nerve in any species of animal so as to generate a model for human persistent neurogenic pain.

4) Claims 1-9 encompass non-surgically (claims 1-9) and surgically (claims 1-4 and 6-9) compressing any nerve wherein the compression causes any sign or symptom of persistent neurogenic pain. The specification has taught that compression of the saphenous nerve by surgical infusion of collagen leads to hyperalgesia (pages 23-24) and that compression of the tibial nerve by non-surgical injection of collagen leads to allodynia (pages 15-17 and 22-23). The

specification has not taught compression of any nerve leading to any sign or symptom of persistent pain. The state of the art at the time of filing was that compression of a nerve does not necessarily result in pain. Lundborg, (1982, Journal of Hand Surgery, Vol. 7, pages 252-259) taught that compression of the medial nerve by non-traumatic, non-surgical infusion of fluid did not cause pain (see paragraph bridging pages 252-253 and page 254, col. 2, lines 10-11). Therefore, compression of any nerve will not necessarily result in persistent neurogenic pain.

The specification has failed to provide the guidance necessary to non-surgically compress any nerve other than the tibial nerve such that a sign or symptom of neurogenic pain is achieved. It is not known how to inject collagen around any nerve other than the tibial nerve without surgical exposure of the nerve as taught by the specification and cause a sign or symptom of persistent pain. The specification further fails to provide the guidance necessary to compress the saphenous, tibial or any other nerve such that any sign or symptom of persistent neurogenic pain is achieved. For example, the specification teaches that compression of the saphenous nerve leads to hyperalgesia and that compression of the tibial nerve leads allodynia. Therefore, it would require undue experimentation to determine how to compress (or alter) any nerve, surgically or non-surgically, such that any sign or symptom of persistent neurogenic pain is achieved.

In view of the breadth of the claims with respect to the genus of animal species and type of nerve alteration and in view of the state of the art with respect to the unpredictability of phenotype of transgenic animals there is insufficient guidance in the specification to make and use the invention as claimed. Thus, for the reasons given above, it would require undue

experimentation for one of skill in the art at the time of filing to implement the invention as claimed with a reasonable degree of success.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 6-9 are unclear because of the placement of the phrase "...in an animal that is a model for human persistent neurogenic pain" (lines 1-2). It is not clear whether the animal is already a model prior to altering the nerve or if it becomes a model for persistent neurogenic pain following nerve alteration. Claims 2-4 depend from claim 1 and are included in this rejection.

Claim 5 is unclear. It is not clear if the term "non-traumatic" is describing the claimed animal as being a non-traumatic animal or that the compression placed around a nerve is done in a non-traumatic manner.

Claims 1-9 are unclear because the metes and bounds of what is encompassed by the phrase "a clinical sign or symptom of a physiologic change in the nerve that is indicative of persistent neurogenic pain" is not known. It is not known whether the phrase encompasses pain or any other symptom that can accompany persistent pain such as sensory latency.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Peterson (Anesthesiology, January 2001, Vol. 94, pages 15-20).

Claim 1 is drawn to a method for producing a nerve alteration in an animal comprising non-traumatically altering a nerve so that a clinical sign or symptom of a physiologic change in the nerve that is indicative of persistent pain is produced in the animal.

Peterson taught a noninvasive and noninjurious human pain model (Abstract lines 2-3; page 16, col. 1, lines 8-11) produced by sequential application of moderate intensity thermal and chemical stimuli (Abstract, lines 3-5) wherein the human pain model is characterized by lowered pain thresholds (allodynia), which is a symptom of a physiologic change in a nerve that is indicative of persistent pain (page 15, col. 2, lines 17-18; page 16, col. 1, lines 8-11; page 19, col. 1, lines 20-27). Allodynia was assessed using the von Frey test, which was the same basis for pain assessment taught by the instant specification (refer to Petersen, page 17, col. 2, lines 19-24, for example and page 21, line 4 of the instant specification, for example).

2) Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Lublin (Prim Care Update Ob/Gyns, 1998, Vol. 5, pages 280-285).

Claim 5 is drawn to an animal model for persistent neurogenic pain wherein compression is placed around a nerve non-surgically.

Lublin teaches human patients with carpal tunnel syndrome, which is an animal model of persistent neurogenic pain, wherein compression develops non-surgically around the median nerve (Abstract; page 280, last paragraph; page 281, col. 2, line 37).

Allowable Subject Matter

The following claims 1 and 5 are drafted by the examiner and considered to distinguish patentably over the art of record in this application, are presented to applicant for consideration:

1. A method of non-traumatically and non-surgically applying direct compression to the tibial nerve of a mammal comprising injecting collagen around the tibial nerve such that the collagen causes compression of the tibial nerve, wherein the mammal exhibits allodynia.

5. A non-human mammal comprising an induced, non-traumatic, non-surgical compression of the tibial nerve wherein the animal exhibits allodynia.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER